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EXAMINER
[illegible]

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ART UNIT	PAPER NUMBER
1804	26

DATE MAILED: 08/26/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on Dec. 21, 1993 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 15-52 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 15-52 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Upon further consideration, the indication of allowability for claim 47, which was suggested by the Examiner in Paper No. 19, is withdrawn. Applicants' arguments have been carefully considered with regard to new grounds of rejection set forth below.

Claims 15-44, 46 and new claims 47-52 remain. Claims 1-14 and 45 are cancelled.

The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office action.

The rejection under 35 U.S.C. 112 second paragraph on page 2 of the previous office action is withdrawn in view of Applicants' amendments and arguments.

Claims 15-44, and 46 remain and new claims 47-52 are rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As recited previously, the claims recite " a Bacillus thuringiensis crystal protein" (Claim 15(a), for example). However, Applicants have enabled the claimed invention for only one B. thuringiensis crystal protein which sequence is shown in Figure 1. Not only do different varieties of B. thuringiensis have different insecticidal proteins with varying homology to each other, but the same variety of B. thuringiensis may have several insecticidal proteins. For example, Thorne et al points out that the subspecies kurstaki crystal contains at least 3 proteins with insecticidal activity (page 801, column 2, top, marked section; see other marked sections as well on pages 801 and 808-809). See also, Hofte et al, especially Tables 1-5.

As recited previously, claims limited to recite characteristics of the insecticidal protein genes described in the present specification might overcome this rejection. Limitation to genes derived from DNA encoding a Bacillus thuringiensis insecticidal crystal protein of about 130 kD (support in specification, page 66, for example) with toxicity to Lepidopteran insects (support in specification, page 64, for example) is suggested. Regarding claim 47, further review of the present specification indicates that there is no basis in the specification for the language "130-135 kD". Consequently, amendment to recite --about 130 kD-- as originally suggested in this ground of rejection, is suggested.

Applicants argue that it would be inequitable to limit the scope of Applicants' claims to the examples disclosed in the specification (Amendment E, page 6, first partial paragraph). This argument is not persuasive because limitation as suggested (i.e., Limitation to genes derived from DNA encoding a Bacillus thuringiensis insecticidal crystal protein of about 130 kD (support in specification, page 66, for example) with toxicity to Lepidopteran insects (support in specification, page 64, for example)) does not limit Applicants' claims to exemplified species, but rather to a major class of B.t. genes (see Hofte et al, Table 1, for example). Recitation of "Bacillus thuringiensis crystal protein insecticide structural gene" (claim 15) is believed to be an inappropriate scope for the invention claimed in light of the teaching of the present specification. Note that other B.t. insecticidal proteins are dissimilar in structure (size of protein produced, DNA sequence of gene, etc.) and in insect specificity to the species exemplified by Applicants (see Hofte et al, Tables 1 and 3, for example). Applicants do not explain why the present specification is enabling for expression of genes in plant cells that encode proteins with different structures and specificities than the species exemplified in the specification. Other B.t. proteins are similar only in that they are toxic to insects. But, in many cases, the insect

toxicity is to an entirely different order of insects (see Hofte et al, especially Tables 1 and 3). Consequently, this rejection is maintained.

With regard to Example 13.2(page 126), and pNSBP544, and Example 14, the present specification does not provide an enabling teaching on the Coleopteran specificity of the insecticidal protein encoded by this and related constructs in plants and plant cells as plant cells are defined by Applicants (present specification, page 48) because Applicants do not provide evidence of the operability of plants expressing B.t.t. with Coleopteran specificity.

The rejection of claims 23, 26-44 and 46 under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to transformed plant cells comprising a gene which encodes a Bacillus thuringiensis crystal protein fragment which includes the first 607 amino acids from the N-terminus of the B.t. protein is withdrawn in favor of the new ground of rejection set forth below. Applicants' arguments have been carefully considered with regard to this new ground of rejection.

Claims 23, 26-44 and 46 remain and 15-16, 18-22, 24-25, and 49-52 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to transformed tomato comprising a gene which encodes a Bacillus thuringiensis crystal protein fragment which includes the first 607 amino acids from the N-terminus of the B.t. protein with toxicity to Manduca sexta in accordance with the teachings of the present specification. See MPEP 706.03(n) and 706.03(z).

As recited previously, it is noted that the Declaration of Guy A. Cardineau et al describes Exhibits 7 and 8 which teach plants transformed with pH585 which is described in the present specification (07/713,624) at page 135, for example. This construct encoded the first 607 amino acids from the N-terminus of the B.t. protein (present specification, page 133). Exhibit 9 which describes potato transformed with a similar construct, falls short of describing plants which are insecticidal. Thus, the claims should be

appropriately limited. The rejection is maintained for the present broadly recited claims as it is not predictable that shorter truncations would be operable.

As recited previously, enablement for plant cells containing such truncated B.t. genes is given the 10/21/88 date as plant cells containing such constructs are not exemplified in the previous specifications. Exemplification is considered necessary for enablement in this case in view of the unpredictability of this art at the time of the claimed invention. Gelvin is relied upon to evidence that the expression of a foreign gene in a plant cell was unpredictable at the time of the claimed invention (see Gelvin, especially pages 356-357, bridging sentence, for example). Furthermore, as a specific example, a full length version of a Bacillus thuringiensis crystal protein toxin was expressed in tomato but was not expressed in tobacco (Compare Vaeck et al, note page 36, column 2, paragraph 2, and Fischhoff et al, note page 810, column 1, top). Therefore, enablement for Applicants' claimed invention is limited to tomato as employed in the example.

Regarding the limitation to Manduca sexta, newly set forth, it is well known that a given B. t. toxin does not show toxicity against all insect species (See Hofte et al, Table 5; Vaeck et al, page 37, column 1, for example). Furthermore, Hickle et al teach that it is not predictable which insect species a given B.t. isolate will be active against (Hickle et al, column 6, lines 14-23). Thus, the specification is not enabling for insects in general, since insects which would be encompassed by the claims as now recited vary considerably and one skilled in the art cannot predict that the B.t. crystal proteins of the present specification would have insecticidal activity against any other class of insect.

Applicants appear to argue that limitation to exemplified species is required and is contrary to patent law (Amendment E, pages 6-7, bridging paragraph). However, the limitation set forth is based upon the information provided by Applicants in the specification and in submitted Declarations.

The present specification is not enabling for all amino acid sequence lengths. That is, there is no teaching that B.t. protein truncations shorter than 607 amino acids will have general insecticidal activity. Likewise, there is no guidance on how to use the C-terminal portion of the protein to obtain plants resistant to all insects. However, this rejection does not limit Applicants' claims to exemplified species but to tomato containing the 607 N-terminal amino acids which includes B.t. toxins with 607 N-terminal amino acids and additional amino acids up to and including full length.

Claims 15-16, 19, 22-26, 28-29, 39-44, and 46 remain and new claims 49, and 51-52 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to dicot cells. See MPEP 706.03(n) and 706.03(z). Applicant's arguments have been fully considered but they are not deemed to be persuasive.

As recited previously, there is no evidence in the specification that the claimed invention is enabled for plant species in general. Plant species vary with respect to their ability to undergo transformation and regeneration.

Applicants argue that regeneration of maize was known as far back as 1982 (Amendment E, page 7, paragraph No. 4). This argument is not persuasive because there is no evidence that the regenerable lines discussed by Hibberd et al were transformable. Likewise, there is no evidence that the transformed callus of Applicants was capable of regeneration. Both transformation and regeneration are necessary to achieve a transformed plant. While Vasil reports that regeneration was known for the Gramineae as of April 1988 (see pages 398-400), transformed cells were recalcitrant to regeneration (see pages 400-401).

Regarding Applicants' arguments with regard to "plant cells", (Amendment E, page 8, first full paragraph), Applicants consider the "cells of the invention [to] include those within plants" (Remarks, page 12, top). Plant cells are defined by Applicants to encompass plants (present specification,

page 48). The present specification and/or Declaration is not enabling for transformed monocot plant cells within plants and it is maintained that transformed monocots could not have been achieved without undue experimentation by one skilled in the art at the time of the claimed invention as evidenced by Vasil.

The rejection of claims 15-46 under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to Bacillus thuringiensis crystal protein genes with toxicity to Lepidopteran insects is withdrawn in favor of the new ground of rejection set forth below. Applicants' arguments have been carefully considered with regard to this new ground of rejection.

Claims 15-44, and 46-52 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to a full length Bacillus thuringiensis crystal protein gene where the insecticide encoding fragment is the insecticide encoding fragment found in any of pH450, pH577, or pH578 and the plant or plant cell is any of tomato, tobacco, or cotton and the toxic activity is directed against Manduca sexta. See MPEP 706.03(n) and 706.03(z). Applicant's arguments have been fully considered but they are not deemed to be persuasive.

A given B. t. toxin does not show toxicity against all insect species (See Hofte et al, Table 5; Vaeck et al, page 37, column 1, for example). Furthermore, Hickle et al teach that it is not predictable which insect species a given B.t. isolate will be active against (Hickle et al, column 6, lines 14-23). Thus, the specification is not enabling for insects in general, since insects which would be encompassed by the claims as now recited vary considerably and one skilled in the art cannot predict that the B.t. crystal proteins of the present specification would have insecticidal activity against any other class of insect.

There is no evidence in the specification that the claimed invention is enabled for all plant species. Expression of a foreign gene in a plant cell is

unpredictable (see Gelvin, especially pages 356-357, bridging sentence, for example). As a specific example, a full length version of a Bacillus thuringiensis crystal protein toxin was expressed in tomato but was not expressed in tobacco (Compare Vaeck et al, note page 36, column 2, paragraph 2, and Fischhoff et al, note page 810, column 1, top). Therefore, enablement for Applicants' claimed invention is limited to tomato, tobacco, or cotton as employed in the examples of the Cardineau Declaration.

Applicants argue that the claimed invention is enabled for any B.t. toxin and that this includes B.t. toxins with specificities to a variety of insects (Amendment E, page 8, paragraph No. 5). This argument is not persuasive because Applicants' claims are deemed to be enabled with respect to a class of B.t. genes, i.e. the family defined by Hofte et al as cryI (see Hofte et al, Table 1, for example). Note that other B.t. insecticidal proteins are dissimilar in structure (size of protein produced, DNA sequence of gene, etc.) and in insect specificity to the species exemplified by Applicants (see Hofte et al, Tables 1 and 3, for example). Applicants do not explain why the present specification should be considered enabling for expression of genes in plant cells that encode proteins with different structures and specificities than the species exemplified in the specification. Other B.t. proteins are similar only in that they are toxic to insects. But, in many cases, the insect toxicity is to an entirely different order of insects (see Hofte et al, especially Tables 1 and 3). Consequently, this rejection is maintained.

Claims 23, 26-27, 29-31, 34, 41-44 and 46 remain and new claims 49-50 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Fischhoff et al.

As recited previously, Fischhoff et al disclose plant and plants cells which were insecticidal due to expression of truncated forms of a B.t. toxin gene. It is noted that Applicants are not entitled to the filing date of the parent application with respect to claims to truncated versions of the B.t. gene (see below).

Claims 23, 26-27, 33, 41-44 and 46 remain new claims 49-50 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Vaeck et al.

Vaeck et al disclose plants and plants cells which were insecticidal due to expression of truncated forms of a B.t. toxin gene. Although Vaeck et al actually uses B.t. sequences from a different strain than that used by Applicants, Applicants' claims are so broadly recited that they are anticipated by Vaeck et al. It is noted that Applicants are not entitled to the filing date of the parent application with respect to claims to truncated versions of the B.t. gene (see below).

Claims 23, 26-27, 29-33, 41-44, and 46 remain and new claims 49-50 are rejected under 35 U.S.C. § 102 (b) as being anticipated by De Greve et al (EP-A 193259, publication date September 3, 1986).

De Greve et al disclose plant and plants cells (tobacco) which were insecticidal due to expression of truncated forms of a B.t. toxin gene. It is noted that the De Greve et al reference predates the parent application 06/848,733. Insecticidal, transformed plants and plant cells with truncated genes are not enabled in the grandparent application 06/535,354.

Claims 15-21, 23-39, 41-44 and 46 remain and new claims 48-52 are rejected under 35 U.S.C. 103 as being unpatentable over either of Vaeck et al or Fischhoff et al taken with Wong et al, Held et al, or Klier et al as applied in the previous office action. Applicants arguments have been carefully considered but are not deemed persuasive.

As recited previously, Vaeck et al and Fischhoff et al disclose plant and plants cells which were insecticidal due to expression of truncated forms of a B.t. toxin gene. Although Vaeck et al actually uses B.t. sequences from a different strain than that used by Applicants, Applicants' claims are so broadly recited that they are obvious over either of Vaeck et al or Fischhoff et al. Furthermore, use of sequences from the same strain as disclosed by

Applicants or other B.t. strains in place of the insecticidal genes employed by Vaeck et al or Fischhoff et al would be obvious in view of the availability of such sequences as taught by Wong et al or Held et al or Klier et al. It is noted that Applicants are not entitled to the filing date of the parent application with respect to claims to truncated versions of the B.t. gene (see below). Therefore, the Vaeck et al and Fischhoff et al references may properly be applied to claims to a truncated B.t. gene expressed in plants.

Claims 15-21, 23-39, 41-44 and 46 remain and new claims 48-52 are rejected under 35 U.S.C. 103 as being unpatentable over De Greve et al (EP-A 193259) taken with Wong et al, Held et al, or Klier et al.

De Greve et al disclose plant and plants cells which were insecticidal due to expression of truncated forms of a B.t. toxin gene. It is noted that the De Greve et al reference predates the parent application 06/848,733. Insecticidal, transformed plants and plant cells and truncated genes are not enabled in the grandparent application 06/535,354. Therefore, application of the De Greve et al reference to the present claims is proper.

While De Greve et al may not use exactly the same insecticidal gene sequences as claimed by Applicants, use of sequences from the same strain as disclosed by Applicants or other B.t. strains in place of the insecticidal genes employed by De Greve et al would be obvious in view of the availability of such sequences as taught by Wong et al or Held et al or Klier et al.

With respect to the 102 and 103 rejections set forth above, Applicants again argue that the first application exemplifies truncated genes at pages 37-39 (Amendment E, page 8, paragraph 6). As set forth previously, this argument is not persuasive as the specification of the first application only teaches expression in bacterial cells, not in plant cells. Furthermore, the truncated construct described in the first application has not been shown to be insecticidal in plants in subsequent applications and/or communications.

Thus, the rejections set forth previously clearly set forth a prima facie case of obviousness which has not been overcome by Applicants' arguments. The rejection is therefore maintained as the insecticidal plant material and methods for producing insecticidal plants and plant cells are obvious over the prior art, absent evidence to the contrary.

Claims 15-44 and 46-52 are rejected under 35 U.S.C. 103 as being unpatentable over De Greve et al (EP-A 193259) taken with Wong et al, Held et al, or Klier et al further taken with Umbeck. De Greve et al disclose plant and plant cells which were insecticidal due to expression of both full length and truncated forms of a B.t. toxin gene. Although the truncated forms worked better than the full length forms, the full length form of the gene also had an insecticidal effect (see, for example, Example 13.2). It is noted that the De Greve et al reference predates the parent application 06/848,733. Insecticidal, transformed plants and plant cells and truncated genes are not enabled in the grandparent application 06/535,354. Furthermore, the constructs of the Cardineau Declaration (paper No. 17) were not taught in the 06/535,354 application. Therefore, application of the De Greve et al reference to the present claims is proper.

While De Greve et al may not use exactly the same insecticidal gene sequences as claimed by Applicants, use of sequences from the same strain as disclosed by Applicants or other B.t. strains in place of the insecticidal genes employed by De Greve et al would be obvious in view of the availability of such sequences as taught by Wong et al or Held et al or Klier et al.

To the extent that Applicants' present claims encompass cotton, they are rendered obvious by the above references further taken with Umbeck. Umbeck provides express motivation to make a B.t. insecticidal cotton plant (see, for example, column 5, lines 39-54). Although the date of the Umbeck reference is after the 06/848,733 application, the '733 application does not

teach cotton. B.t. insecticidal cotton plants are given the date of the 07/260,574 application which is the first of Applicants' filings to exemplify cotton, although operability was not established until the Cardineau Declaration (paper No. 17).

Upon further consideration, the Cardineau Declaration has been deemed to be insufficient to overcome the above rejection for the claims as so broadly recited. In view of the unpredictability of expression of B.t. in plant cells as discussed above under 35 USC 112, the Cardineau Declaration, which is drawn to tobacco, tomato, potato, maize and cotton, is insufficient for the claims presented here which are to all plants, and broad categories of plants i.e., dicot plants, monocot plants and plants susceptible to transformation by Agrobacteria tumefaciens.

Consequently, the modification of the methods for producing insecticidal plants and plant cells taught by De Greve et al using other B.t. toxin genes was well within the ordinary skill in the art at the time the claimed invention was made as adequately demonstrated by the secondary and tertiary references. One of ordinary skill would have had a reasonable expectation of success in view of the availability of B.t. sequences as indicated by the references and the guidelines provided by De Greve et al. Thus the claimed invention as a whole was clearly prima facie obvious over the references, in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 15-44 and 46-52 are rejected under 35 U.S.C. 103 as being unpatentable over Bevan et al, Fraley et al, Herrera-Estrella et al, or Barton et al. taken with Wong et al, Held et al, or Klier et al et al further in view of Brinster et al. The primary references teach cloning and expressing foreign genes in plant cells by using a DNA vector having a plant expressible promoter (e.g. the T-DNA nopaline synthetase promoter) controllably linked to a foreign gene. Additionally, Bevan et al and Herrera-Estrella et al teach regeneration of plants from single cells. The secondary references teach the

cloning and expression of insecticidal structural genes. Brinster et al teach fusing a foreign structural gene to the promoter sequence of an eukaryotic DNA in a eukaryotic cell so as to enable expression of the foreign gene in the resulting eukaryotic organism.

Consequently, the modification of the methods taught by the primary references with known sequences was well within the ordinary skill in the art at the time the claimed invention was made as adequately demonstrated by the secondary and tertiary references. One of ordinary skill would have had a reasonable expectation of success in expressing insecticidal B.t. toxin genes in plant cells in view of the cited references. Thus the claimed invention as a whole was clearly prima facie obvious over the references, in the absence of sufficient, clear, and convincing evidence to the contrary.

No claim is allowed.

The following allowable claim is suggested for the purpose of an interference:

A tomato plant which has been regenerated from a tomato plant cell transformed to comprise a full length Bacillus thuringiensis crystal protein gene capable of encoding a Bacillus thuringiensis crystal protein of about 130 kD under control of a promoter such that said gene is expressible in said plant in amounts insecticidal to Lepidopteran insects.

The suggested claims must be copied exactly, although other claims may be proposed under 37 C.F.R. § 1.605(a).

APPLICANT SHOULD MAKE THE SUGGESTED CLAIM WITHIN ONE MONTH FROM THE DATE OF THIS LETTER. FAILURE TO DO SO WILL BE CONSIDERED A DISCLAIMER OF THE SUBJECT MATTER OF THIS CLAIM UNDER THE PROVISIONS OF 37 C.F.R. § 1.605(a). THE EXTENSION OF TIME PROVISIONS OF 37 C.F.R. § 1.136(a) DO NOT APPLY TO THIS TIME PERIOD.

Claims 15-44 and 46-52 are considered unpatentable over the above suggested claim.

An inquiry concerning this communication should be directed to Che Swyden Chereskin, Ph.D., at telephone number (703) 308-1180. Inquiries of a general nature should be directed to the Group 180 secretary at (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

CHE S. CHERESKIN
PRIMARY EXAMINER
GROUP 1800

Che Swyden Chereskin
8/20/93